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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,762	12/27/2005	Massimo Ferrari	207,385	8763
7590 09/04/2007				
Jay S Cinamon		EXAMINER		
Abelman Frayne & Schwab		MABRY, JOHN		
10th Floor				
666 Third Avenue		ART UNIT		
New York, NY 10017		PAPER NUMBER		
		1609		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/562,762

Applicant(s)

FERRARI ET AL.

Examiner

John Mabry

Art Unit

1609

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 27 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 26-45 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26-45 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 12/27/2005 & 2/08/2006
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

There are two Information Disclosure Statements filed that contains identical references on the following dates: 12/27/2005 and 2/8/2006.

### ***Objections***

The specification is objected to because there are structures missing and cut off on the following pages: bottom of page 3, bottom of page 4 and bottom of page 5. Correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 29, 37, and 40, the phrases "preferably" and "possibly" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The term "D(0.9)", "D(0.5) and "D[4.3]" in claims 44 and 45 are relative terms which render the claim indefinite. The term "D(0.9)", "D(0.5) and "D[4.3]" is not defined

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by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What does Applicant intend by this term? What is the meaning of these terms?

The term "in the presence or tributylamine" in claim 28 is a relative term which renders the claim indefinite. The term "in the presence or tributylamine " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. There appears to be a typo. The Examiner will treat as "of".

The term "OCOCH<sub>3</sub>-" in formula VI of claim 26 is a relative term which renders the claim indefinite. The term "OCOCH<sub>3</sub>-" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Is bonding to the phenyl ring through the methyl group? Where does Applicant intend for the point of attachment?

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 26-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (US 4,358,593) in view of Jones et al (EP62503) and in further view of Alt (US 5,523,416).

The instant application claims a process for the preparation of raloxifene hydrochloride by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene. The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene without isolating the product. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the

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corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride).

***Scope & Content of Prior Art MPEP 2141.01***

Jones et al (US 4,358,593 – see entire disclosure) discloses a process for the preparation of raloxifene hydrochloride by reaction of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene with acetylating agent, particularly acetic anhydride in the presence of 4-dimethylaminopyridine (but also teaches the use of triethyl amine, see column 3, lines 34-43), to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (see column 9, Preparation 2). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene hydrochloride in which a small portion was recrystallized to from ethanol to provide an analytical sample. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene was then deprotected by treatment of sodium hydroxide in methanol, followed by acidification to pH 2-3 then readjusted to basic pH 8 which resulted in 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene (raloxifene) (see column 12, lines 36-65, Example 9).

***Differences between Prior Art & the Claims MPEP 2141.02***

Jones et al (US 4,358,593) differs from the instant invention in that Jones does not disclose the direct synthesis of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride). However, Jones et al suggests that during the deprotection of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene to 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene (raloxifene), it is convenient to form the salts by reacting the 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene (raloxifene) with a suitable acid wash in the final step of the synthesis to achieve high yields of corresponding salt. The suitable acid is preferably hydrochloric acid (see column 8, lines 8-30).

Jones et al differs also from the instant invention in that Jones does not disclose the synthesis of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene by demethylation of the starting material 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene.

However, Jones et al (EP62503) teaches that 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene can undergo acylation with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride to form the protected intermediate which can eventually be synthesized to the desired product (see page 2, line 25 – page 4, line 6).

Additionally, Alt (US 5,523,416) has also shown that 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene can be deprotected with pyridine hydrochloric acid to make the 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (see column 14, lines 61-67 through column 15, lines 1-9, Example 2).

***Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413***

It would be obvious to one of ordinary skill in the art at the time when the invention was made to initiate the synthesis of the desired final product, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride) by Jones' (US 4,358,593) procedure by changing the starting material, 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene, which is taught in the EP62503 reference in the process of making the same compound.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 5,512,684 A discloses related synthetic processes of formula I as described in above rejection.

Claims 26-45 stand rejected.



**Conclusion**


Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

  
JM

**RITA DESAI  
PRIMARY EXAMINER**

  
8/30/07